Topic 20 – Heart failure, cardiomyopathy – A

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0199

Endoglin is required to maintain normal cardiac function in adult life

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Endoglin protein (also known as CD105) is a co-receptor for members of the transforming growth factor-β (TGFβ) superfamily of ligands, and regulates angiogenesis. Patients carrying mutations in the endoglin gene develop the inherited vascular dysplasia, Hereditary Haemorrhagic Telangiectasia (HHT). In light of the growing clinical interest in endoglin function in cardiovascular disease, we aimed to determine its role by depleting endoglin in a mouse model during adult life and assess effects on cardiac function. Endoglin was depleted in adult Rosa26-Cre-ERT2;Engfl/fl mice using tamoxifen treatment to generate "ubiquitous" endoglin knockout (Eng-iKOu) mice and cardiac magnetic resonance imaging (MRI) was used to evaluate cardiac function at 1, 3, 5 and 12 weeks after endoglin knockdown. Loss of endoglin leads to an enlarged heart and cardiomyocyte hypertrophy within 5 weeks and left ventricular volumes continued to enlarge substantially over subsequent weeks. However, LV ejection fraction was not significantly altered in Eng-iKOu mice compared with controls suggesting that cardiac function was not impaired. To address whether the cardiac remodelling observed in Eng-iKOu mice was due to loss of endoglin in endothelial cells we used a transgenic Cre line (Cdh5Cre-ERT2) to generate endothelial specific depletion of endoglin (Eng-iKOe). These mice showed a similar increase in heart mass and ventricular volumes to the Eng-iKOu mice. To investigate if vasomotor defects are contributing to the major cardiac remodelling, we analysed vasomotor function in the aortas of Eng-iKOe mice. We found an increased contraction response of the aorta to phenylephrine in Eng-iKOe mice compared to controls, suggesting that endoglin is important in controlling the aortic contractile response. These results describe a novel phenotype and highlight the importance of endothelial endoglin in the maintenance of cardiac structure and function.

0237

Gadd45 γ promotes cardiac dysfunction by inducing necroptosis pathway in a mouse model of chronic myocardial infarction

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Background: Postinfarction remodeling is accompanied and influenced by perturbations in MAPK signaling. The Growth arrest and DNA-damage-inducible 45 (Gadd45) proteins are small acidic proteins involved in DNA repair and modulation of MAPK activities. Despite its relationship with p38 MAPK, little is known about the role of Gadd45 in the heart. Our aim is to explore the potential contribution of Gadd45 gamma (γ) on heart failure development after myocardial infarction (MI).

Methods and results: MI was induced in wild-type (WT) versus Gadd45 γ (KO) mice by left anterior descending coronary artery ligation. Pre-MI, WT, and KO hearts had comparable chamber dimensions and ventricular function, but as early as 1 week post-MI, KO mice had significantly better cardiac function than WT mice. The left ventricular dilatation, dysfunction and fibrosis remained better in the KO mice throughout the study (4 weeks). We examined the infarct size following a 24-hour MI and found it to be decreased in the KO mice. In addition, necroptosis activity pathway (RIP1; caspase 8) was reduced in the KO mice. To mimic the Gadd45 γ overexpression observed during MI, we injected 3 10^11 of cTNT-Gadd45 γ AAV9 particles i.v. and studied the cardiac function. Four weeks after the cTNT-Gadd45 γ AAV9 injection, we observed a decrease in the cardiac function compared to the GFP-AAV9 injected control mice. A remodeling process is engaging with more fibrosis. Gadd45 γ overexpression activated the necroptosis pathway through p38 MAPK.

Conclusion: Gadd45 γ promotes ischemic injury, accentuates post-MI remodeling and left ventricular dysfunction, and increases the progression to heart failure. The lost of gadd45 γ confers resistance to ischemic injury, at least in part, via limiting necroptosis pathway through a p38 MAPK dependant mechanism. This work, demonstrate the importance of Gadd45 γ/p38 MAPK complex in the development of heart failure, particularly in the balance of the cell death process.

0310

Assay development and high-throughput screening to identify PDE2A activators to treat heart failure

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Chronic activation of β-adrenergic (β-AR) pathway causes excessive accumulation of cAMP in cardiomyocytes and participates in pathological cardiac remodeling leading to heart failure (HF). Cyclic nucleotide phosphodiesterases (PDEs) are responsible for the degradation of cAMP and cGMP in subcellular compartments. Among the different PDE families, PDE2 is unique in being activated ~5-fold by cGMP, thus mediating a negative cross talk between cGMP and cAMP signaling. Recently, we found that PDE2A activity is increased in human HF and this may represent a protective mechanism limiting β-AR cardiotoxicity in chronic HF. Our therapeutic strategy is to target PDE2 with specific activators to treat HF at the early stages. A PDE2 activity assay has been developed, first using a purified PDE2 from bovine adrenal glands, then using a commercial recombinant protein (full-length human PDE2A). We miniaturized a bioluminescent activity assay in 384 well plates, which was validated for High-Throughput Screening (HTS) with an excellent Z-factor (>0.7) on the Ciblot HTS platform. Moreover, an in silico screening based on the binding of molecules on the GAF-B domain (regulatory domain) of PDE2 has been performed on a large library of molecules. As a counter screen, a PDE4 assay has been employed to eliminate nonspecific modulators. Ranking of hits is based on activation efficacy in comparison to 5 µM cGMP, EC50, Emax and cytotoxicity following chemical resynthesis in a SAR (Structure Activity Relationship) strategy. Several complementary assays are currently under development to confirm the effect of the activators in a Hit to Lead process (cellular assays, cAMP ELISA, co-cristallisation, Biacore). This challenging project is supported by LabEx LERMIT within its new cardiovascular target program

0149

Agonistic anti β3-adrenoceptor antibodies do not affect the β1-adrenoceptor-mediated inotropy and the β3 adrenoceptor-mediated vasorelaxation in Lewis rat

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